Synthesis of enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-2-alkyl-1-phenylsulfonylcyclopropanes using Bakers' yeast

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Reduction of the ketone 1 with Bakers' yeast gives the alcohol (*R*)-2 with high enantiomeric excess, and this upon subsequent epoxidation and alkylation with Grignard reagents provides the alcohols (*S*)-4 without racemisation. Tosylation of the alcohols (*S*)-4 under common conditions yields the tosylates (toluene-*p*-sulfonates) (*S*)-5, whilst under Mitsunobu conditions inversion of configuration takes place giving the tosylates (*R*)-5. Subsequent treatment of the tosylates (*S*)-5 and (*R*)-5 with lithium diisopropylamide leads to cyclization affording the enantiomerically pure cyclopropanes (*S*,*S*)-6 and (*R*,*R*)-6 in high yields, respectively. The diastereoisomeric alcohol (*S*)-4f, obtained by methylation of the alcohol (*S*)-4e, can also be converted into the single stereoisomer (*R*,*R*)-6f in enantiomerically pure form.

Introduction

An enantiomerically pure cyclopropane ring system is a common feature in a wide variety of natural products,[1] and a number of methods are available for its construction.[2] As an addition to the armoury of sulfur-based reagents available to synthetic chemists,[3–6] we here report the synthesis of enantiomerically pure cyclopropanes containing a sulfonyl group by means of Bakers' yeast (BY) reduction.

BY-mediated reduction of ketones has been widely used, because it is cheap, versatile, and easy to perform.[7,8] However, it is impossible to obtain both isomers of the enantiomeric alcohols, and high chemical yields and enantiomeric excesses (ee) cannot always be expected.

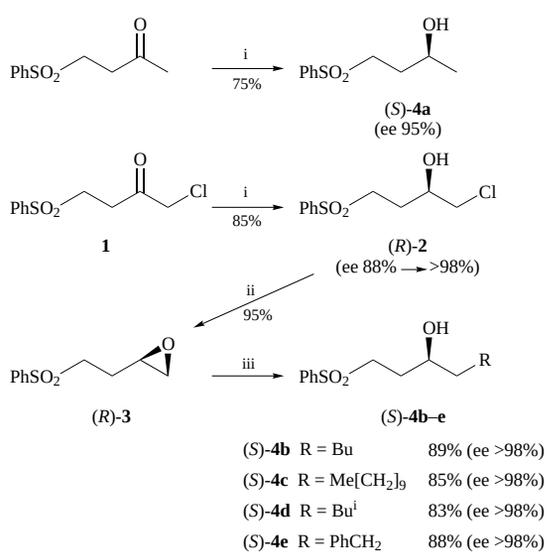
Results and discussion

Since there have been many reports relating enantioselective reduction of ketones containing a sulfur atom with BY,[9–12] we first tried to prepare (3*S*)-1-phenylsulfonylalkan-3-ols (*S*)-**4** directly from the corresponding ketones. Reduction of 1-phenylsulfonylbutan-3-one with BY readily afforded (3*S*)-1-phenylsulfonylbutan-3-ol (*S*)-**4a** in 93% ee. The *S*-configuration was determined as follows; alkylation of the dianion generated from (*S*)-**4a** with 1-iodononane, and subsequent reductive desulfonylation with Raney nickel led to the formation of tridecan-2-ol having the same configuration as authentic (2*S*)-tridecan-2-ol.[13] However, 1-phenylsulfonyloctan-3-one was found to be unreactive towards BY.

In order to obtain an alcohol with high enantiomeric purity in good yield, a ketone, in which one of the groups bonded to a carbonyl group is much smaller than the other, must be employed as a starting substrate. Hence we tried to obtain (3*R*)-4-chloro-1-phenylsulfonylbutan-3-ol (*R*)-**2** from 4-chloro-1-phenylsulfonylbutan-3-one **1**.

Compound **1** was prepared efficiently by 1,4-addition of benzenethiol to 4-chlorobut-1-en-3-one, followed by oxidation. A suspension of the ketone **1**, BY, and sucrose was stirred at 30 °C for 5 days. After extraction of the resulting alcohol with ethyl acetate, chromatography on silica gel gave the product (*R*)-**2** as a solid in 85% yield (88% ee); this upon recrystallization from hexane–ethyl acetate readily yielded the alcohol (*R*)-**2** in enantiomerically pure form. The *R*-configuration was determined by comparison of an authentic specimen of the alcohol (*S*)-**4a** with that formed by reductive dechlorination of the alcohol (*R*)-**2** with tributyltin hydride and 2,2′-azoisobutyronitrile (AIBN).

Treatment of the alcohol (*R*)-**2** with sodium hydroxide in methanol generated (3*S*)-3,4-epoxy-1-phenylsulfonylbutane (*R*)-**3** in 95% yield. To a solution of Grignard reagents in tetrahydrofuran (THF) was added copper(I) iodide, followed by a solution of the epoxide (*R*)-**3** in THF; this resulted in formation of the alcohols (*S*)-**4** in high yields and >98% ee (Scheme 1).



Scheme 1 *Reagents:* i, Bakers' yeast, H_2O; ii, NaOH, MeOH; iii, RMgBr, CuI, THF

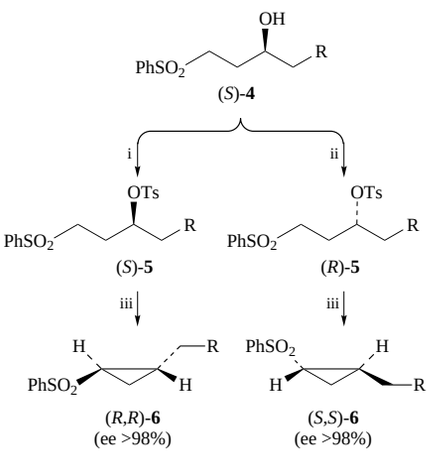
Tosylation of the alcohols (*S*)-**4** in the presence of pyridine readily gave the tosylates (toluene-*p*-sulfonates) (*S*)-**5** with retention of configuration (Method i, Scheme 2). Since BY reduction generally proceeds by Prelog's rule,[14] it is impossible to obtain both enantiomers (*S*)-**4** and (*R*)-**4** at the same time. In order to remove these defects tosylation under Mitsunobu conditions was attempted by appropriate modification of the experimental procedure in the literature.[15,16] In an improved procedure the alcohols (*S*)-**4** were treated with zinc tosylate in refluxing benzene to give the tosylates (*R*)-**5** with inversion of configuration in high yields and ees (Method ii, Scheme 2). These results are shown in Table 1.

Treatment of the tosylates (*S*)-**5** with lithium diisopropyl-

Table 1 Preparation of the tosylates (*S*)-**5** and (*R*)-**5**

	R	Yield (%)[a]	$[\alpha]_D$ (MeOH)
(*S*)-**5a**	H	80	−23.17[c]
(*S*)-**5b**	Bu	85	−13.91
(*S*)-**5c**	$Me[CH_2]_9$	84	−11.70
(*S*)-**5d**	Bu^i	96	−10.47
(*S*)-**5e**	$PhCH_2$	81	+15.00[b]
(*R*)-**5a**	H	74	+25.61[c]
(*R*)-**5b**	Bu	85	+12.33
(*R*)-**5c**	$Me[CH_2]_9$	74	+11.76
(*R*)-**5d**	Bu^i	79	+10.43
(*R*)-**5e**	$PhCH_2$	80	−12.36[b]

[a] Isolated yield. [b] In Acetone. [c] $[\alpha]_{546}$.



Scheme 2 *Reagents:* i, TsCl, pyridine; ii, $(TsO)_2Zn$, DEAD, Ph_3P, benzene; iii, LDA, THF

amide (LDA) in THF readily led to cyclization giving (1*R*,2*R*)-2-alkyl-1-phenylsulfonylcyclopropanes (*R*,*R*)-**6** in >98% ee. The enantiomeric excess was determined by HPLC analysis using a chiral column.

^{1}H NMR measurements showed that the alkyl and sulfonyl groups were in a *trans* configuration. The mixture of diastereoisomers (*R**,*R**)-**6a** and (*R**,*S**)-**6a** was formed by an alternative method; namely, cyclization of 2-methyl-1,3-di(phenylthio)propane[17] followed by oxidation. The stereochemical assignment for the cyclopropane (*R**,*R**)-**6a** was made in comparison with the diastereoisomer (*R**,*S**)-**6a**.

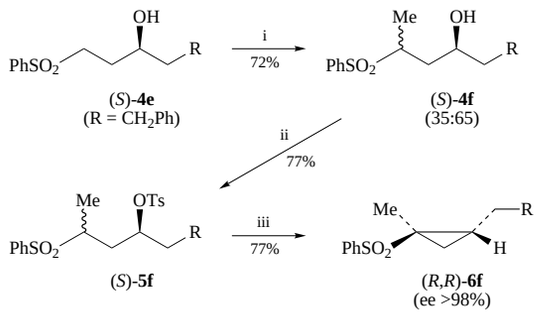
On similar treatment of the tosylates (*R*)-**5** the enantiomeric cyclopropanes (*S*,*S*)-**6** were synthesized in >98% ee. These findings mean that carbon–carbon bond formation proceeded with complete stereochemical inversion. These results are shown in Table 2.

In order to obtain 1,2-dialkylcyclopropane, (4*S*)-6-phenyl-2-phenylsulfonyl-4-(*p*-tosyloxy)hexane (*S*)-**5f** was prepared as follows: the dianion generated from the alcohol (*S*)-**4e** was treated with iodomethane to give a diastereoisomeric mixture (35:65) of the methylated compound (*S*)-**4f**, which was subsequently converted into the tosylates (*S*)-**5f** (diastereoisomeric ratio, 35:65) in the customary manner. Cyclization of the tosylate (*S*)-**5f** by use of LDA afforded enantiomerically pure (1*R*,2*R*)-1-methyl-2-(2-phenylethyl)-1-phenylsulfonylcyclopropane (*R*,*R*)-**6f** in 80% yield. The stereochemical assignment for the cyclopropane (*R*,*R*)-**6f** was made on the basis of NOE observation between the CH_2CH_2Ph and *Me* groups. Interestingly, neither the diastereoisomeric (1*S*,2*R*)-isomer nor the enantiomeric (1*S*,2*S*)-isomer was detected. Since the interconversion between the (1*S*,2*R*)- and (1*R*,2*R*)-isomers is actually impossible during the reaction, the present finding means that stereochemical inversion occurred at the C-3 atom of the tosylate (*S*)-**5f**; at the same time, the stereoconvergence took place at the stable carbanion adjacent to the sulfonyl group of this compound. Further investigation of this phenomena is now in progress.

Table 2 Preparation of the cyclopropanes (*R*,*R*)-**6** and (*S*,*S*)-**6**

	R	Yield (%)[a]	$[\alpha]_D$ (MeOH)
(*R*,*R*)-**6a**	H	64	−38.52[b]
(*R*,*R*)-**6b**	Bu	85	+5.56
(*R*,*R*)-**6c**	$Me[CH_2]_9$	80	+6.59
(*R*,*R*)-**6d**	Bu^i	98	−6.82
(*R*,*R*)-**6e**	$PhCH_2$	98	−5.26
(*S*,*S*)-**6a**	H	59	+33.75[b]
(*S*,*S*)-**6b**	Bu	95	−5.57
(*S*,*S*)-**6c**	$Me[CH_2]_9$	85	−6.67
(*S*,*S*)-**6d**	Bu^i	92	+7.41
(*S*,*S*)-**6e**	$PhCH_2$	92	+5.58

[a] Isolated yield. [b] $[\alpha]_{549}$.



Scheme 3 *Reagents:* i, BuLi (2 equiv.), MeI, THF; ii, TsCl, Pyridine; iii, LDA, THF

In conclusion, we have demonstrated the efficient preparation of both enantiomers of cyclopropanes containing a sulfonyl group. Since a sulfonyl group may be converted into other functional groups,[3–6,18] the present strategy may be widely applicable to organic synthesis.

Experimental

General

NMR spectra were recorded with a JEOL JNM-A-400 (400 MHz) or a JEOL JNM-GX-270 (270 MHz) spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. IR spectra were taken on a Shimadzu FT-IR-8600 instrument. Optical rotations were determined with a JASCO DIP-370 polarimeter and are recorded in 10^{-1} deg cm^2 g^{-1}. HPLC analyses were carried out with a Shimadzu LC-6A machine equipped with a ODS, a PYE, or a chiral cellulose column (Daicel CHIRALPAX OB-H). Column chromatography was performed with Wakogel 200 silica gel, and TLC with Merck silica gel 60 F_{254}. THF was freshly distilled from calcium hydride before use, and the pyridine was dried over KOH. Other solvents were dried over molecular sieves and reagents used as received. Bakers' yeast (BY) was obtained from the Oriental Yeast Co. 4-Chlorobut-1-en-3-one was prepared according to literature procedures.[19]

Preparation of 4-chloro-1-phenylsulfonylbutan-3-one 1

Triethylamine (1 cm^3) was added to a stirred solution of 4-chlorobut-1-en-3-one (10.5 g, 100 mmol) in benzenethiol (11.0 g, 100 mmol) and benzene (100 cm^3) at 0 °C, and the mixture was stirred at room temperature for 10 h after which it was diluted with water (50 cm^3). The organic phase was separated, washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was dissolved in methanol (200 cm^3) containing $Na_2WO_4 \cdot 2H_2O$ (0.3 g, 1.0 mmol), and to the stirred solution was added dropwise 30% aqueous H_2O_2 (24.9 g, 220 mmol) at 0 °C. The resultant solution was allowed to warm to room temperature over a period of 1 h after which it was stirred at this temperature for 10 h. The reaction mixture was then diluted with water (50 cm^3) and extracted with ethyl acetate (2 × 150 cm^3). The extract was washed with brine, dried

($MgSO_4$), and evaporated to dryness. The crude product was recrystallized from hexane–ethyl acetate (1:1, v/v) to give the pure product **1** (19.7 g, 80%) as a colourless solid, mp 107 °C; ν_{max}(Nujol/cm^{-1}) 1730 (C=O), 1320 (SO_2) and 1140 (SO_2); δ_H($CDCl_3$) 3.12 (2 H, t, *J* 8, SO_2CH_2), 3.44 (2 H, t, *J* 8, $SO_2CH_2CH_2CO$), 4.11 (2 H, s, $COCH_2Cl$) and 7.56–7.96 (5 H, m, PhH).

Preparation of (3*R*)-4-chloro-1-phenylsulfonylbutan-3-ol (*R*)-2

A suspension of the ketone **1** (9.86 g, 40 mmol), BY (160 g) and sucrose (40 g) in water (1 dm^3) was stirred at 30 °C for 2 days, after which time BY (40 g) and sucrose (10 g) were added to it. The resultant suspension was further stirred at 30 °C for additional 3 days and then filtered. The filtrate was extracted with ethyl acetate (3 × 150 cm^3), and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and freed of solvent *in vacuo*. Column chromatography [silica gel; eluent hexane–ethyl acetate (2:1)] of the residue gave the product (*R*)-**2** (8.45 g, 85%) in 88% ee. The enantiomerically pure alcohol (*R*)-**2** was obtained as a colourless solid by recrystallization (hexane–ethyl acetate), mp 95 °C; $[\alpha]_D^{21}$ +18.25 (*c* 1.03 in MeOH); ee >98%; ν_{max}(Nujol/cm^{-1}) 3500 (OH), 1300 (SO_2) and 1145 (SO_2); δ_H($CDCl_3$) 1.83–2.10 (2 H, m, $SO_2CH_2CH_2$), 2.56–2.65 (1 H, br, OH), 3.18–3.41 (2 H, m, SO_2CH_2), 3.44–3.62 (2 H, m, $ClCH_2$), 3.91–3.98 (1 H, m, CH) and 7.27–7.96 (5 H, m, PhH) (Found: C, 48.0; H, 5.0. Calc. for $C_{10}H_{13}O_3ClS$: C, 48.3; H, 5.2%).

Preparation of (3*S*)-1-phenylsulfonylbutan-3-ol (*S*)-4a [11]

Treatment of 1-phenylsulfonylbutan-3-one (8.48 g, 40 mmol) in a similar fashion to that described above gave the product (*S*)-**4a** as a colourless solid in 93% ee. Recrystallization (hexane–ethyl acetate) of the crude product afforded the alcohol (*S*)-**4a** (6.42 g, 75%); $[\alpha]_D^{25}$ +15.05 (*c* 0.93 in MeOH); ee >98%.

Determination of the absolute configuration of the alcohol (*S*)-4a

To a stirred solution of the alcohol (*S*)-**4a** (0.86 g, 4.00 mmol) in dry THF (15 cm^3) was added dropwise butyllithium (1.67 mol dm^{-3} in hexane; 5.00 cm^3, 8.40 mmol) at −80 °C under Ar; stirring was continued for 30 min after which 1-iodononane (1.22 g, 4.80 mmol) was added slowly to the mixture. The resultant solution was stirred at −80 °C for 30 min and then allowed to warm to room temperature over a period of 2 h. After the reaction had been quenched with saturated aqueous NH_4Cl, the aqueous layer was separated and extracted with ethyl acetate (30 cm^3). The combined organic phase and extract were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by column chromatography [silica gel; eluent hexane–ethyl acetate (3:1)] to afford (2*S*)-4-phenylsulfonyltridecan-2-ol (11.6 g, 85%).

A mixture of the above alcohol (0.31 g, 0.90 mmol) and Raney nickel (W-2) (2.5 g) in dry ethanol (15 cm^3) was refluxed for 90 h. After work-up as described above, column chromatography [silica gel; eluent hexane–ethyl acetate (3:1)] gave (2*S*)-tridecan-2-ol (0.07 g, 39%) as a colourless liquid; $[\alpha]_D^{28}$ +6.80 (*c* 1.32 in MeOH) (lit.,[13] $[\alpha]_D^{28}$ +7.22).

Preparation of (3*R*)-3,4-epoxy-1-phenylsulfonylbutane (*R*)-3

To a stirred solution of the alcohol (*R*)-**2** (7.46 g, 30 mmol) in methanol (50 cm^3) was added dropwise a solution of NaOH (1.32 g, 33.0 mmol) in methanol (60 cm^3) at 0 °C. The solution was further stirred at 0 °C for 30 min and then at room temperature for 2 h; it was then diluted with water (150 cm^3) and extracted with ethyl acetate (2 × 70 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by column chromatography [silica gel; eluent hexane–ethyl acetate (1:1)] to afford the product (*R*)-**3** (6.01 g, 95%) as a viscous liquid; $[\alpha]_D^{24}$ +12.96 (*c* 1.19 in MeOH); ν_{max}(neat/cm^{-1}) 3064 (OH), 1304 (SO_2), 1234 (epoxy) and 1150 (SO_2); δ_H($CDCl_3$) 1.76–1.89 (1 H, m, OCH_2), 2.10–2.23 (1 H, m, OCH_2), 2.50 (1 H, m, OCH), 2.78–3.27 (2 H, m, $SO_2CH_2CH_2$), 3.27 (2 H, t, *J* 12, SO_2CH_2) and 7.56–7.95 (5 H, m, PhH).

Preparation of the alcohols (*S*)-4b–e

Typical procedure. A Grignard reagent was prepared from 1-bromo-2-methylpropane (2.88 g, 21 mol) and Mg (0.51 g, 21 mmol) in dry THF (35 cm^3) at room temperature under Ar in the customary manner and was cooled to 0 °C. To the stirred solution was added CuI (1.33 g, 7.0 mmol), and then dropwise a solution of the epoxide (*R*)-**3** (1.48 g, 7.0 mmol) in dry THF (10 cm^3); the resulting mixture was stirred for 2 h. After the reaction mixture had been treated with saturated aqueous NH_4Cl (50 cm^3), the aqueous layer was separated and extracted with ethyl acetate (2 × 70 cm^3). The combined organic phase and extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography [silica gel; eluent hexane–ethyl acetate (3:1)] provided (3*S*)-6-methyl-1-phenylsulfonylheptan-3-ol (*S*)-**4d** (1.53 g, 83%) as a viscous liquid; $[\alpha]_D^{27}$ +11.49 (*c* 0.87 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 3528 (OH), 1306 (SO_2) and 1148 (SO_2); δ_H($CDCl_3$) 0.86 (6 H, d, *J* 6, 2 Me), 1.06–1.54 (5 H, m, 2 CH_2 and CH), 1.67–2.01 (2 H, m, $SO_2CH_2CH_2$), 2.27 (1 H, m, OCH), 3.14–3.39 (2 H, m, SO_2CH_2), 3.63–3.65 (1 H, br, OH) and 7.54–7.93 (5 H, m, PhH) (Found: C, 62.7; H, 8.3. Calc. for $C_{14}H_{22}O_3S$: C, 62.2; H, 8.2%).

(3*S*)-1-Phenylsulfonyloctan-3-ol (*S*)-4b. The product (*S*)-**4b** was isolated as a viscous liquid (89%); $[\alpha]_D^{24}$ +8.74 (*c* 0.87 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 3524 (OH), 1304 (SO_2) and 1150 (SO_2); δ_H($CDCl_3$) 0.86 (3 H, t, *J* 7, Me), 1.22–1.43 (8 H, m, 4 CH_2), 1.66–1.99 (2 H, m, $SO_2CH_2CH_2$), 2.46 (1 H, s, CH), 3.14–3.39 (2 H, m, SO_2CH_2), 3.64–3.67 (1 H, br, OH) and 7.53–7.93 (5 H, m, PhH) (Found: C, 61.7; H, 8.4. Calc. for $C_{14}H_{22}O_3S$: C, 62.2; H, 8.2%).

(3*S*)-1-Phenylsulfonyltetradecan-3-ol (*S*)-4c. The product (*S*)-**4c** was isolated as a viscous liquid (85%); $[\alpha]_D^{24}$ +7.62 (*c* 0.84 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 3504 (OH), 1290 (SO_2) and 1144 (SO_2); δ_H($CDCl_3$) 0.88 (3 H, t, *J* 7, Me), 1.25–1.41 (20 H, m, 10 CH_2), 1.69–1.99 (2 H, m, $SO_2CH_2CH_2$), 2.01 (1 H, s, CH), 3.15–3.38 (2 H, m, SO_2CH_2), 3.66–3.68 (1 H, br, OH) and 7.54–7.93 (5 H, m, PhH) (Found: C, 68.0; H, 9.5. Calc. for $C_{20}H_{34}O_3S$: C, 67.8; H, 9.7%).

(3*S*)-5-Phenyl-1-phenylsulfonylpentan-3-ol (*S*)-4e. The product (*S*)-**4e** was isolated as a colourless solid (88%); $[\alpha]_D^{28}$ +9.52 (*c* 0.84 in MeOH); ee >98%; ν_{max}(Nujol/cm^{-1}) 3320 (OH), 1306 (SO_2) and 1148 (SO_2); δ_H($CDCl_3$) 1.22–1.41 (4 H, m, 2 CH_2), 1.92 (1 H, m, CH), 2.60–2.81 (2 H, m, CH_2), 3.15–3.36 (2 H, m, SO_2CH_2), 3.71–3.74 (1 H, br, OH) and 7.13–7.94 (10 H, m, 2 PhH) (Found: C, 67.5; H, 6.5. Calc. for $C_{17}H_{20}O_3S$: C, 67.1; H, 6.6%).

Preparation of the tosylates (*S*)-5a–e

General procedure. To a stirred solution of the alcohol (*S*)-**4d** (0.27 g, 1.0 mmol) in dry pyridine (6.0 cm^3) was added *p*-tosyl chloride (TsCl) (0.38 g, 2.0 mmol) at 0 °C under Ar; stirring continued for 1 day after which further TsCl (0.38 g, 2.0 mmol) was added to the mixture. The solution was further stirred at 0 °C for an additional 1 day after which it was quenched with water (100 cm^3) and extracted with diethyl ether (2 × 80 cm^3). The combined extracts were washed with dilute hydrochloric acid and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography [silica gel; eluent hexane–ethyl acetate (3:1)] gave the product (3*S*)-6-methyl-1-phenylsulfonyl-3-tosyloxyheptane (0.41 g, 96%) as a viscous liquid; $[\alpha]_D^{27}$ −10.47 (*c* 0.86 in MeOH); ν_{max}(neat/cm^{-1}) 1366 (OSO_2), 1310 (SO_2), 1176 (OSO_2) and 1150 (SO_2); δ_H($CDCl_3$) 0.75 (6 H, d, *J* 4, 2 Me), 0.95–1.04 (4 H, m, CH_2), 1.32–1.45 (1 H, m, CH), 1.47–1.58 (2 H, m, $SO_2CH_2CH_2$), 2.43 (3 H, s, Ar*Me*), 3.00–3.19 (2 H, m, SO_2CH_2), 4.54–4.63 (1 H, m, SO_2OCH) and 7.27–7.91 (9 H, m, PhH and ArH).

(3*S*)-1-Phenylsulfonyl-3-tosyloxybutane (*S*)-5a. The product (*S*)-**5a** was isolated as a viscous liquid (80%); $[\alpha]_{546}^{23}$ −23.17 (*c*

0.82 in MeOH); ν_{max}(neat/cm^{-1}) 1356 (OSO_2), 1308 (SO_2), 1178 (OSO_2) and 1150 (SO_2); δ_H($CDCl_3$) 1.23 (3 H, d, *J* 8, Me), 1.96–2.17 (2 H, m, CH_2), 2.44 (3 H, s, Ar*Me*), 2.95–3.19 (2 H, m, SO_2CH_2), 4.70 (1 H, q, *J* 8, SO_2OCH) and 7.31–7.94 (9 H, m, PhH and ArH).

(3*S*)-1-Phenylsulfonyl-3-tosyloxyoctane (*S*)-5b. The product (*S*)-**5b** was isolated as a colourless solid (85%); $[\alpha]_D^{26}$ −13.91 (*c* 0.92 in MeOH); ν_{max}(Nujol/cm^{-1}) 1360 (OSO_2), 1310 (SO_2), 1176 (OSO_2) and 1150 (SO_2); δ_H($CDCl_3$) 0.81 (3 H, t, *J* 5, Me), 1.13–1.29 (6 H, m, 3 CH_2), 1.43–1.56 (2 H, m, CH_2), 1.92–2.15 (2 H, m, CH_2), 2.44 (3 H, s, Ar*Me*), 3.00–3.19 (2 H, m, SO_2CH_2), 4.56–4.65 (1 H, m, SO_2OCH) and 7.27–7.96 (9 H, m, PhH and ArH).

(3*S*)-1-Phenylsulfonyl-3-tosyloxytetradecane (*S*)-5c. The product (*S*)-**5c** was isolated as a viscous liquid (84%); $[\alpha]_D^{26}$ −11.70 (*c* 0.94 in MeOH); ν_{max}(neat/cm^{-1}) 1360 (OSO_2), 1308 (SO_2), 1176 (SO_2) and 1150 (OSO_2); δ_H($CDCl_3$) 0.89 (3 H, t, *J* 5, Me), 1.12–1.31 (18 H, m, 9 CH_2), 1.48–1.52 (2 H, m, CH_2), 1.94–2.14 (2 H, m, CH_2), 2.44 (3 H, s, Ar*Me*), 3.00–3.19 (2 H, m, SO_2CH_2), 4.56–4.65 (1 H, m, SO_2OCH) and 7.27–7.90 (9 H, m, PhH and ArH).

(3*S*)-5-Phenyl-1-phenylsulfonyl-3-tosyloxypentane (*S*)-5e. The product (*S*)-**5e** was isolated as a colourless solid (81%); $[\alpha]_D^{28}$ +15.00 (*c* 0.80 in acetone); ν_{max}(Nujol/cm^{-1}) 1344 (OSO_2), 1304 (SO_2), 1168 (OSO_2) and 1144 (SO_2); δ_H($CDCl_3$) 1.76–1.91 (2 H, m, CH_2), 1.96–2.14 (2 H, m, CH_2), 2.44 (3 H, s, Ar*Me*), 2.99–3.19 (2 H, m, SO_2CH_2), 4.60–4.69 (1 H, m, SO_2OCH) and 6.99–7.90 (14 H, m, 2 PhH and ArH).

Preparation of the tosylates (*R*)-5a–e

Typical procedure. Diethyl azodicarboxylate (DEAD) (0.96 g, 5.50 mmol) was added slowly to a stirred mixture of the alcohol (*S*)-**4d** (0.27 g, 1.00 mmol), triphenylphosphine (1.31 g, 5.00 mmol) and zinc tosylate (0.24 g, 0.6 mmol) in dry benzene (20 cm^3) at 50 °C. The resultant mixture was stirred at 50 °C for 30 min and then 35 °C for 10 h after which it was quenched with dilute hydrochloric acid (10 cm^3). The mixture was extracted with dichloromethane (2 × 70 cm^3) and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and filtered. After being concentrated, purification of the residue by column chromatography [silica gel; eluent hexane–ethyl acetate (4:1)] yielded (3*R*)-6-methyl-1-phenylsulfonyl-3-tosyloxyheptane (*R*)-**5d** (0.33 g, 79%) as a viscous liquid; $[\alpha]_D^{25}$ +10.43 (*c* 0.92 in MeOH).

(3*R*)-1-Phenylsulfonyl-3-tosyloxybutane (*R*)-5a. The product (*R*)-**5a** was isolated as a viscous liquid (74%); $[\alpha]_{546}^{23}$ +25.61 (*c* 0.82 in MeOH).

(3*R*)-1-Phenylsulfonyl-3-tosyloxyoctane (*R*)-5b. The product (*R*)-**5b** was isolated as a colourless solid (85%); $[\alpha]_D^{26}$ +12.33 (*c* 0.92 in MeOH).

(3*R*)-1-Phenylsulfonyl-3-tosyloxytetradecane (*R*)-5c. The product (*R*)-**5c** was isolated as a viscous liquid (78%); $[\alpha]_D^{26}$ +11.76 (*c* 0.91 in MeOH).

(3*R*)-5-Phenyl-1-phenylsulfonyl-3-tosyloxypentane (*R*)-5e. The product (*R*)-**5e** was isolated as a colourless solid (80%); $[\alpha]_D^{24}$ −12.36 (*c* 1.00 in acetone).

Preparation of the cyclopropanes (*R*,*R*)-6a–e and (*S*,*S*)-6a–e

Typical procedure. A solution of lithium diisopropylamide (LDA) was prepared from diisopropylamine (1.09 g, 10.8 mmol) and butyllithium (1.67 mol dm^{-3} in hexane; 6.47 cm^3, 10.8 mmol) in dry THF (5 cm^3) in the customary manner and was added dropwise to a stirred solution of the tosylate (*S*)-**5d** (3.77 g, 9.0 mmol) in dry THF (30 cm^3) at −80 °C under Ar. The resulting solution was stirred for 30 min and then allowed to warm to room temperature over 2 h. After being stirred for an additional 8 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 cm^3), and the aqueous phase was separated and extracted with ethyl acetate (2 × 80 cm^3). The combined organic phase and extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography [silica gel; eluent hexane–ethyl acetate (5:1)] of the residue gave (1*R*,2*R*)-2-(3-methylbutyl)-1-phenylsulfonylcyclopropane (*R*,*R*)-**6d** (2.22 g, 98%) as a viscous liquid; $[\alpha]_D^{28}$ −6.82 (*c* 0.88 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 2928, 1448, 1309 (SO_2), 1148 (SO_2) and 914 (cyclo-CH); δ_H($CDCl_3$) 0.79 (6 H, d, *J* 4, 2 Me), 0.84–0.92 (1 H, m, $PhSO_2CHCH\mathit{H}$), 1.05–1.20 (3 H, m, RCH_2 and $C\mathit{H}Me_2$), 1.33–1.53 (3 H, m, CH_2 and $PhSO_2CHC\mathit{H}H$), 1.60–1.70 (1 H, m, $RCH_2C\mathit{H}$), 2.15–2.22 (1 H, m, $PhSO_2C\mathit{H}$) and 7.29–7.92 (5 H, m, PhH) (Found: C, 65.8; H, 7.9. Calc. for $C_{14}H_{20}O_2S$: C, 66.6; H, 8.0%).

(1*R*,2*R*)-2-Methyl-1-phenylsulfonylcyclopropane (*R*,*R*)-6a. The product (*R*,*R*)-**6a** was isolated as a viscous liquid (64%); $[\alpha]_{546}^{22}$ −38.52 (*c* 1.16 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 2972, 1448, 1306 (SO_2), 1148 (SO_2) and 922 (cyclo-CH); δ_H($CDCl_3$) 0.84 (1 H, ddd, *J* 5.2, 6.3, 8.0, $PhSO_2CHCH\mathit{H}$), 1.11 (3 H, d, *J* 6.1, Me), 1.47 (1 H, ddd, *J* 5.2, 4.7, 4.9, $PhSO_2CHC\mathit{H}H$), 1.72–1.82 (1 H, m, $MeC\mathit{H}$), 2.18 (1 H, ddd, *J* 4.4, 4.7, 8.0, $PhSO_2C\mathit{H}$) and 7.52–7.92 (5 H, m, PhH) (Found: C, 61.3; H, 6.4. Calc. for $C_{10}H_{12}O_2S$: C, 61.2; H, 6.2%).

(1*R*,2*R*)-2-Pentyl-1-phenylsulfonylcyclopropane (*R*,*R*)-6b. The product (*R*,*R*)-**6b** was isolated as a viscous liquid (85%); $[\alpha]_D^{22}$ +5.56 (*c* 0.72 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 2928, 1448, 1306 (SO_2), 1150 (SO_2) and 928 (cyclo-CH); δ_H($CDCl_3$) 0.80–0.91 (3 H, m, CH_2 and $PhSO_2CHCH\mathit{H}$), 1.11–1.27 (9 H, m, Me and 3 CH_2), 1.35–1.42 (1 H, m, $PhSO_2CHC\mathit{H}H$), 1.62–1.74 (1 H, m, $RCH_2C\mathit{H}$), 2.15–2.21 (1 H, dm, *J* 8.6, $PhSO_2C\mathit{H}$) and 7.52–7.92 (5 H, m, PhH) (Found: C, 66.2; H, 8.1. Calc. for $C_{14}H_{20}O_2S$: C, 66.6; H, 8.0%).

(1*R*,2*R*)-2-Undecanyl-1-phenylsulfonylcyclopropane (*R*,*R*)-6c. The product (*R*,*R*)-**6c** was isolated as a viscous liquid (80%); $[\alpha]_D^{25}$ +6.59 (*c* 0.91 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 2928, 1467, 1306 (SO_2), 1146 (SO_2) and 920 (cyclo-CH); δ_H($CDCl_3$) 0.84–0.91 (3 H, m, CH_2 and $PhSO_2CHCH\mathit{H}$), 1.12–1.39 (21 H, m, Me and 9 CH_2), 1.47–1.54 (1 H, m, $PhSO_2CHC\mathit{H}H$), 1.64–1.72 (1 H, m, $RCH_2C\mathit{H}$), 2.14–2.21 (1 H, dm, *J* 8.8, $PhSO_2C\mathit{H}$) and 7.52–7.92 (5 H, m, PhH) (Found: C, 71.2; H, 9.6. Calc. for $C_{20}H_{32}O_2S$: C, 71.4; H, 9.6%).

(1*R*,2*R*)-2-(2-Phenylethyl)-1-phenylsulfonylcyclopropane (*R*,*R*)-6e. The product (*R*,*R*)-**6e** was isolated as a viscous liquid (98%); $[\alpha]_D^{27}$ −5.26 (*c* 0.95 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 2928, 1448, 1306 (SO_2), 1150 (SO_2) and 928 (cyclo-CH); δ_H($CDCl_3$) 0.83–0.91 (1 H, m, $PhSO_2CHCH\mathit{H}$), 1.43–1.83 (4 H, m, CH_2, $PhSO_2CHC\mathit{H}H$ and $RCH_2C\mathit{H}$), 2.21–2.27 (1 H, dm, *J* 8.6, $PhSO_2C\mathit{H}$), 2.52–2.61 (2 H, t, *J* 7.3, Ph′CH_2), 7.08–7.29 (5 H, m, Ph′H) and 7.52–7.91 (5 H, m, PhH) (Found: C, 71.6; H, 6.3. Calc. for $C_{17}H_{18}O_2S$: C, 71.3; H, 6.3%).

(1*S*,2*S*)-2-Methyl-1-phenylsulfonylcyclopropane (*S*,*S*)-6a. The product (*S*,*S*)-**6a** was isolated as a viscous liquid (59%); $[\alpha]_{546}^{22}$ +33.75 (*c* 0.63 in MeOH); ee >98%.

(1*S*,2*S*)-2-Pentyl-1-phenylsulfonylcyclopropane (*S*,*S*)-6b. The product (*S*,*S*)-**6b** was isolated as a viscous liquid (95%); $[\alpha]_D^{22}$ −5.57 (*c* 0.79 in MeOH); ee >98%.

(1*S*,2*S*)-2-Undecanyl-1-phenylsulfonylcyclopropane (*S*,*S*)-6c. The product (*S*,*S*)-**6c** was isolated as a viscous liquid (85%); $[\alpha]_D^{22}$ −6.67 (*c* 0.84 in MeOH); ee >98%.

(1*S*,2*S*)-2-(3-Methylbutyl)-1-phenylsulfonylcyclopropane (*S*,*S*)-6d. The product (*S*,*S*)-**6d** was isolated as a viscous liquid (92%); $[\alpha]_D^{25}$ +7.41 (*c* 0.81 in MeOH); ee >98%.

(1*S*,2*S*)-2-(2-Phenylethyl)-1-phenylsulfonylcyclopropane (*S*,*S*)-6e. The product (*S*,*S*)-**6e** was isolated as a viscous liquid (67%); $[\alpha]_D^{22}$ +5.88 (*c* 0.68 in MeOH); ee >98%.

Preparation of (4*S*)-6-phenyl-2-phenylsulfonylhexan-4-ol (*S*)-4f

To a stirred solution of (*S*)-**4e** (1.45 g, 4.80 mmol) in dry THF (30 cm^3) was added dropwise butyllithium (1.67 mol dm^{-3} in hexane; 6.35 cm^3, 10.6 mmol) at −80 °C under Ar. Stirring was continued for 30 min after which iodomethane (1.16 g, 7.50 mmol) was added dropwise to the mixture. The resultant solution was stirred at −80 °C for 30 min and then allowed to

warm to room temperature over a period of 2 h, before being treated with saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate (2×80 cm^3), and the combined organic phase was washed with brine, dried ($MgSO_4$), filtered and concentrated. Subsequent column chromatography [silica gel; eluent hexane–ethyl acetate (4:1)] provided the product (*S*)-**4f** (1.09 g, 72%), a viscous liquid, as a 35:65 mixture of diastereoisomers (HPLC); ν_{max}(neat/cm^{-1}) 3524 (OH), 1302 (SO_2) and 1146 (SO_2); δ_H($CDCl_3$) 1.23 (3 H, d, *J* 7.0, Me), 1.62–1.84 (4 H, m, 2 CH_2), 2.07–2.19 (1 H, m, CH), 2.61–2.80 (2 H, m, CH_2), 3.37–3.44 (1 H, m, CH), 3.95 (1 H, br, OH), 7.15–7.32 (5 H, m, Ph′H) and 7.52–7.92 (5 H, m, PhH) (Found: C, 68.2; H, 7.0. Calc. for $C_{18}H_{22}O_3S$: C, 67.9; H, 6.9%).

Preparation of (4*S*)-6-phenyl-2-phenylsulfonyl-4-tosyloxyhexane (*S*)-5f

Reaction of a diastereoisomeric mixture of the alcohol (*S*)-**4f** (0.71 g, 2.20 mmol), TsCl (0.38 g, 2.00 mol) and pyridine (6.0 cm^3) was performed according to the procedure described in the preparation of the tosylate (*R*)-**5d**. The product (*S*)-**5f** (0.78 g, 77%) was isolated as a mixture of diastereoisomers [ratio = 35:65 (HPLC)]; ν_{max}(neat/cm^{-1}) 1358 (OSO_2), 1306 (SO_2), 1176 (OSO_2) and 1148 (SO_2); δ_H($CDCl_3$) 1.18 (3 H, d, *J* 7.0, Me), 1.64–1.93 (4 H, m, 2 CH_2), 2.37–2.57 (2 H, m, CH_2), 2.44 (3 H, s, Ar*Me*), 3.26–3.33 (1 H, m, CH), 4.88–4.95 (1 H, m, SO_2OCH) and 6.98–7.90 (14 H, m, PhH, Ph′H and ArH).

Preparation of (1*R*,2*R*)-1-methyl-2-(2-phenylethyl)-1-phenylsulfonylcyclopropane (*R*,*R*)-6f

According to the procedure described in the preparation of the cyclopropane (*R*,*R*)-**6d**, a diastereoisomeric mixture of the tosylate (*S*)-**5f** (0.47 g, 1.00 mmol) and LDA (1.20 mmol) in dry THF (10 cm^3) gave the product (*R*,*R*)-**6f** (0.23 g, 77%) as a viscous liquid. The other diastereoisomer (1*S**,2*R**)-1-methyl-2-(2-phenylethyl)-1-phenylsulfonylcyclopropane was not detected; $[a]_D^{26}$ −4.37 (*c* 0.87 in MeOH); ee >98%; ν_{max}(neat/cm^{-1}) 2932, 1448, 1302 (SO_2), 1144 (SO_2) and 915 (cyclo-CH); δ_H($CDCl_3$) 0.50 (1 H, dd, *J* 6.0, 5.5, $PhSO_2CHCH$*H*), 1.32 (3 H, s, Me), 1.62–1.71 (3 H, m, CH_2 and $PhSO_2CHC$*H*H), 1.92–2.01 (1 H, m, CH), 2.54–2.70 (2 H, m, Ph′C*H*$_2$), 7.12–7.31 (5 H, m, Ph′H) and 7.51–7.90 (5 H, m, PhH) (Found: C, 72.2; H, 7.0. Calc. for $C_{18}H_{20}O_2S$: C, 71.9; H, 6.7%).

Determination of the enantiomeric excess (ee)

Treatment of the alcohols (*R*)-**2** and (*S*)-**4a**–**e** with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA chloride) and 4-dimethylaminopyridine in the customary manner gave the corresponding MTPA esters in quantitative yields. The enantiomeric excesses of the alcohols were determined by HPLC measurements of the MTPA esters. The ees of the cyclopropanes (*R*,*R*)-**6a**–**f** and (*S*,*S*)-**6a** were, however, determined directly by HPLC analyses using a chiral column [Daicel CHIRALPAX OB-H].

References

1 H.-W. Liu and C. T. Walsh, in *The Chemistry of the Cyclopropyl Group*, ed. by Z. Rappoport, Wiley, Chichester, 1987, p. 959.
2 R. C. Larock, in *Comprehensive Organic Transformations*, VCH Publisher, New York, 1989, p. 71.
3 K. Tanaka and A. Kaji, in *The Chemistry of Sulphones and Sulphoxides*, ed. by S. Patai, Z. Rappoport and C. Stirling, Wiley, New York, 1988, p. 759.
4 N. S. Simpkins, in *Sulphones in Organic Synthesis*, Pergamon Press, Oxford, 1993.
5 P. Metzner and A. Thuillier, in *Sulfur Reagents in Organic Synthesis*, Academic Press, London, 1994.
6 G. H. Whitham, in *Organosulfur Chemistry*, Oxford Science Publications, Oxford, 1995.
7 S. Servi, *Synthesis*, 1990, 1.
8 R. Csuk and B. I. Glänzer, *Chem. Rev.*, 1991, **91**, 49.
9 R. Tanikaga, K. Hosoya and A. Kaji, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1799.
10 T. Fujisawa, E. Kojima, Y. Itoh and T. Sato, *Tetrahedron Lett.*, 1985, **26**, 6089, and references therein.
11 H. Liu and T. Cohen, *J. Org. Chem.*, 1995, **60**, 2022.
12 For a report of asymmetric synthesis of phenylsulfonylalkanols using other enzymes see R. Chinchilla, C. Nájera, J. Pardo and M. Yus, *Tetrahedron: Asymmetry*, 1990, **1**, 575; T. Sugai, Y. Ohtsuka and H. Ohta, *Chem. Lett.*, 1996, 233; A. Svatos, Z. Hunková, V. Kren, M. Hoskovec, D. Saman, I. Valterová, J. Vrkoc and B. Koutek, *Tetrahedron: Asymmetry*, 1996, **7**, 1285.
13 J. D. McClure, *J. Org. Chem.*, 1967, **32**, 3888.
14 V. Prelog, *Pure and Appl. Chem.*, 1964, **9**, 119.
15 O. Mitsunobu, *Synthesis*, 1981, 1.
16 I. Galynker and W. C. Still, *Tetrahedron Lett.*, 1982, **23**, 4461.
17 K. Tanaka, H. Uneme, S. Matsui, R. Tanikaga and A. Kaji, *Chem. Lett.*, 1980, 287.
18 Y.-H. Chang and H. W. Pinnick, *J. Org. Chem.*, 1978, **43**, 374.
19 J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.*, 1948, 278.

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